Abstract ISCTM 2019

Subject To Change: Subject Variability From Early Phase 2 to Late Phase 3 Clinical Trials

Shiovitz TM[1,2], Steinmetz CB[1], Steinmiller BL[1], Golden FR[1]
[1]CTSdatabase LLC, Sherman Oaks, CA; [2]California Neuroscience Research, Sherman Oaks, CA;

Methodological Question Being Addressed: Can study design and execution account for the changing nature of subjects in Phase 3 studies?

Introduction: Duplicate and professional subjects are a significant problem in clinical trials. This problem has been well-characterized in CNS and pain studies, especially in Schizophrenia and Major Depression. These subjects may magnify inclusion criteria, be deceptive about exclusion criteria, and are often non-adherent with study medication. Subject registries are available to detect these duplicate and professional subjects and mitigate their effects on safety and efficacy signal detection. Previously at ISCTM, we shared early data showing an increase in inappropriate subjects during the second half of enrollment in phase 3 studies.

Frequently, smaller Phase 2 studies are positive and even though the same design is used, these large, costly Phase 3 studies are negative. We hypothesize that, not only have the size of the studies changed, but the nature of study subjects has also changed. More inappropriate subjects may arise as a program moves through Phases 2 and 3.

Methods: 6,997 subjects were entered into CTSdatabase, representing seven completed Phase 2 and five completed Phase 3 studies in schizophrenia, MDD, BED, fibromyalgia and ADHD between November 2013 and November 2018. Each study was divided by quartile of enrollment and examined for the number of duplicate, professional or inappropriate subjects that were excluded from the study by the subject registry. Then all quartile data was pooled and tested for significance.

Results: Significantly more inappropriate subjects, Phase 2 and 3 combined, were excluded from studies during the second half of enrollment (102/3571 vs 63/3426 in the first half), p=.006. This was especially evident in Phase 3, where progressively increasing numbers of inappropriate subjects were found with each quartile of enrollment. A significantly greater percentage of Phase 3 subjects (123/4610, 2.7%) were excluded by the registry compared with Phase 2 subjects (42/ 2387, 1.8%), p =.022.

Conclusion: Duplicate and professional subjects are a problem in CNS studies, affecting both safety and efficacy signals. The inappropriate subjects appear to occur more in Phase 3 than in Phase 2 studies, and more in the second half of enrollment in both phases. In the design and execution of Phase 3 studies, factors that produce inappropriate subjects should be appreciated and the appropriate mitigation strategies (e.g. accounting for inappropriate subjects in sample size, duplicate subject detection, nonadherence technologies and resisting the urge to enroll on time at any cost) could be implemented.